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ORIGINAL ARTICLE

Malignancies associated with GIST: a retrospective study with molecular analysis of *KIT* and *PDGFRA*

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Abstract

Purpose Gastrointestinal stromal tumors (GISTs) are the most common soft tissue tumors of the GI tract. Studies have been published reporting additional neoplasms in GIST patients. This study aimed to evaluate possible associations of mutation type, morphology, and clinical aspects of GISTs.

Methods All cases of GIST were identified from our pathology files. Coding exons of *KIT* and *PDGFRA* in GISTs with additional malignancies were sequenced.

Results A total of 70 of 188 (37%) retrieved patients with confirmed diagnosis of GIST showed at least one additional malignant neoplasm. Fifty of these GISTs were located in the stomach (71%), 8 in the small intestine (11%), 5 in the colon/rectum (7%), and 7 cases (6.2%) were of undetermined sites of origin. The distribution of identified mutations was similar to that described in GISTs without secondary malignancies. A total of 37 of 57 cases (65%) showed mutations in the *KIT* gene exon 11, 3 (5%) cases in exon 9, and 1 (2%) case in exon 13. Nine tumors (16%) had mutations of the *PDGFRA* gene. *KIT* and PDGFRA wild-type status were found in seven cases (12%). Most of the secondary neoplasms were located within the GI tract (34%), in the urogenital system (24%), or the breast/female genital tract (20%).

Conclusion This study confirms the high rate of additional malignant tumors in GIST patients. GIST features in these cases are very similar to those with sole GIST.

Keywords Gastrointestinal stromal tumor · GIST · Mutation · Additional/secondary malignancy · *KIT* · PDGFRA

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common soft tissue tumors occurring within the GI tract. [3, 17]

Their incidence is estimated at 7 to 15 cases per 1 million per year [17, 22]. GISTs tend to show a variable clinical course of disease ranging from lesions with no risk of progression to highly aggressive malignant neoplasms with metastatic spread [10]. To stratify their expected behavior, the risk is measured by the most widely accepted scoring system according to Miettinen and Lasota which takes into account the tumor size, the mitotic index in 5 mm^2, and anatomic site [13, 14].

The molecular aberrations in GIST are well characterized: *KIT* and *PDGFRA* mutations account for approximately 80 and 5–10% of all molecular aberrations, respectively, while mutations in genes other than these are rare [9, 13, 15].

Recently, we and others found a noteworthy number of patients who are not only suffering from GIST but also from at least one additional malignancy that was/is diagnosed

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before/after or synchronous to the GIST itself. This issue was addressed by some studies varying in size and an even larger number of case reports in the literature before [1, 2, 5–8, 11, 16, 18–21, 23]. However, only a few studies included molecular analyses and included benign neoplasms. Thus, there are only a small number of studies that have focused on the molecular characterization of GISTs with associated additional malignancies [6, 8].

This study aimed to evaluate the rate of GISTs cases with at least one additional malignancy in our cohort of GISTs and to search for conventional clinicopathological factors and molecular aberrations that might be associated with the occurrence of such secondary malignancies. Additionally, we planned to evaluate the histogenesis and distribution of the malignancies associated with gastrointestinal stromal tumors (MaG).

Patients and methods

Case collection

We screened our pathology information system for GISTs diagnosed within the years 1998 to 2017. These cases were matched with the data of the Clinical and Population-Based Cancer Registry Augsburg (TUZ) to identify cases with an additional neoplasm(s) and to receive follow-up data. Additionally, we screened our clinic information system to complete missing clinical information and follow-up data. Of 188 GIST cases, 70 cases (37%) suffered from at least one additional malignancy according to TUZ data. A total of 67 GIST cases were histologically proven GISTs (or GIST metastases) diagnosed at our department (Fig. 1). In the three cases, the information of the existence of a GIST in the patients' history came from the TUZ. Concerning the time sequence, synchronous tumors were defined as being diagnosed within 1 month (= 30 days). This study was approved by the internal review board of the Klinikum Augsburg.

Immunohistochemistry and molecular analysis

Histologic diagnosis of the GISTs was based on morphology and immunohistochemistry (CD34, S-100, SMA, CD117, DOG-1). Missing CD-117 immunostaining was completed (CD-117, clone YR 145, 1:100 dilution, Cell Marque, Rocklin, California, USA) whenever paraffin material was available. All reactions were developed using the Ventana Ultravision detection system on Ventana BenchMark Ultra staining machine (Roche Diagnostics, Mannheim, Germany). Sanger sequencing was used for sequence analysis. Briefly, after extraction of genomic DNA from FFPE slices using the Maxwell® 16 FFPE Plus LEV DNA Purification Kit (Promega), the dideoxynucleotide sequencing of *KIT* exon 9, 11, 13, and 17 and PDGFRA exon 18 was

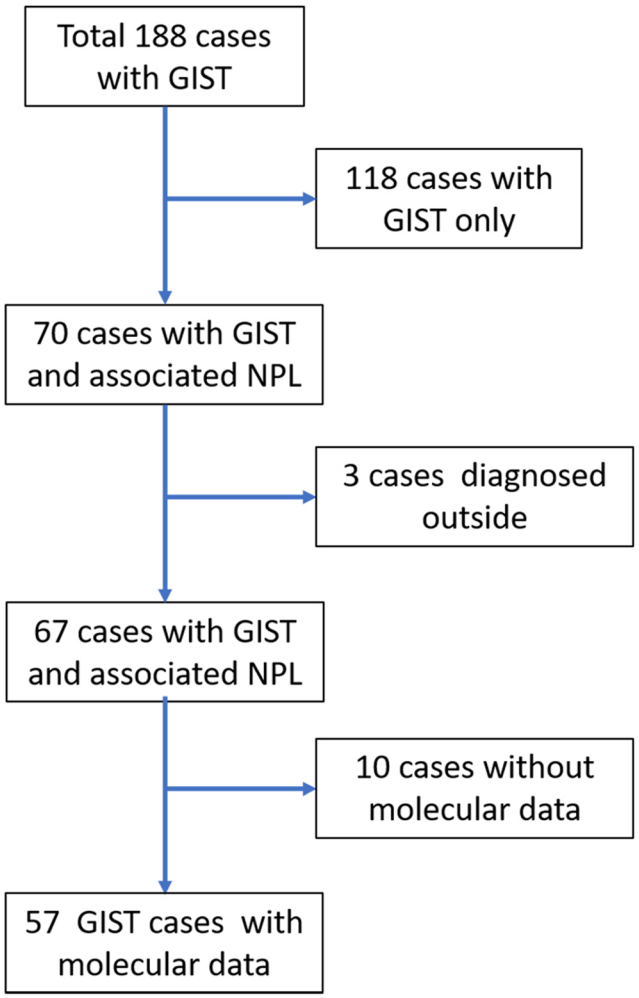

Fig. 1 Case selection. NPL = neoplasm

performed in PCR reactions using AmpliTaqGold® (Life Technologie, Thermo Fisher Scientific, Waltham, MA USA) and specific primers (*KIT* Exon 9 (forward: GAT GCT CTG CTT CTG TAC TG; reverse: GCC TAA ACA TCC CCT TAA ATT GG), *KIT* Exon 11 (forward: CCA GAG TGC TCT AAT GAC TG; reverse: ACC CAA AAA GGT GAC ATG GA), and PDGFRA Exon 18 (forward: TAC AGA TGG CTT GAT CCT GAG T; reverse: AGT GAA GGA GGA TGA GCC TG)). PCR products were sequenced with BigDye® Terminator 1.1 Cycle Sequencing Kit (Life Technologies) on an Applied Biosystems® ABI310 (Life Technologies) according to the manufacturer's instructions. In total, molecular analysis of 55 cases was performed. Risk stratification was performed according to Miettinen and Lasota [13, 14].

Statistics

Statistical analysis was accomplished by use of IBM's SPSS version 24 software suite. Significance was estimated at $P \leq 0.05$. Q-Q-diagrams were used for analysis of normality of

ages at diagnosis. A *t* test was used for comparison of mean values. Cross-table comparison with chi-square analysis was performed toward analyses of subgroups (secondary tumor site, location, origin, and molecular status, morphologic aspects, and site of GIST), and in cases of small numbers, Fisher's exact test was used. Spearman's ratio was used for correlation analyses. Additionally, Kaplan-Meier as well as log-rank analyses were performed for survival analyses.

Results

Pathological features of GIST

The GIST diagnoses were confirmed by experienced pathologists based on defined morphological criteria and immunohistochemical expression of CD117 and/or DOG1. Exclusion of other differential diagnoses was performed by different panels of markers like Melan-A, Desmin, S100, GLUT1, GFAP, etc.

The main pathological features including histological type, location, mitotic count, size, and risk stratification are summarized in Table 1. Mean and median follow-ups were 106 months (± 98) and 84 months from the day of the first diagnosis of malignancy to last time of clinical appearance, respectively. Mean and median overall survival time for GIST with MaG were 70 months (± 95) and 35 months starting from diagnosis of first malignant tumor (GIST or secondary malignancy) until death from any cause, respectively. The collectives of GIST without and GIST with MaGs cases showed significant differences concerning mean age ($P = 0.003$), the rate of occurrence in the small intestine ($P = 0.003$), and risk classifications ($P = 0.010$). In general, the GIST with MaGs showed lower aggressive features compared to GISTs without associated malignancies.

Molecular analysis of GIST

In total, 57 GIST (85% of all GIST cases with MaG) cases were analyzed for mutational status of *KIT* and PDFGFRA. Molecular analysis failed in 13 cases because no amplifiable DNA could be extracted from the archival FFPE material. Seven cases were wild-type (12%) for *KIT* and PDGFRA. Mutation analysis revealed 37 cases harboring mutations of *KIT* exon 11 (65%), 3 cases in *KIT* exon 9 (5%), and 1 case in *KIT* exon 13 (2%). PDGFRA exon 18 mutations were found in seven cases (12%) and PDGFRA exon 12 mutations in two cases (4%) (Table 2) (Fig. 2a).

Out of 50 mutant GIST cases, 20 cases (40% of mutations) showed point mutations, 17 cases (34%) had deletions, and 5 cases (10%) had duplications. In eight cases (16%), more detailed information was not available besides affected genes/exons.

Characteristics of MaGs

Most patients suffered from an additional malignancy of the GI tract, the urogenital system, and from breast/female tract. The exact numbers, the distribution of the other tumors, and the molecular aberrations of the corresponding GISTs are given in Table 2.

There were 13 patients (20.0% of all cases) suffering from more than one additional malignancy; of these, five patients (7.7% of all cases) developed three additional malignancies. Details including the molecular aberrations of the corresponding GISTs are given in Table 3. There was a marginally significant difference concerning the rate of third and fourth neoplasms depending on the site of the secondary tumor ($P = 0.046$) with higher rates for cases where secondary neoplasms originated from the breast/female genital tract and urogenital tract (Fig. 2b).

Grouping according to *KIT* and non-*KIT* mutations revealed a non-significant trend toward a higher rate of non-*KIT* mutations in GISTs with associated tumors from the urogenital tract ($P = 0.083$).

Time sequence

Regarding the time intervals between GIST and secondary malignancies, our data show that GIST was diagnosed synchronously with MaGs in 16 cases (23.0%), before additional malignancy in 21 cases (30%) and after a different malignancy in 32 cases (46%). Time of diagnosis of GIST and additional malignancy were missing for one case (1% of all cases). The distribution of the sequences of the first MaG (metachronous previous/secondary synchronous) was considerably different depending on their origin (Fig. 2b). For example, colorectal cancers were mainly identified synchronously while this occurred in renal cancers in only one single case. In all the other cases, the renal neoplasm preceded the GIST. When GISTs were diagnosed after additional malignancy, mean time interval was 85 months (± 110), and the median interval was 50 months. If GISTs were diagnosed before the MaGs, mean and median time intervals were 36 months (± 29.8) and 29 months, respectively (Fig. 2d) ($P = 0.231$).

Grouping according to *KIT* and non-*KIT* mutations revealed no difference was found regarding the time sequence of the neoplasms ($P = 0.778$).

Discussion

The overall frequency of MaGs in patients with GISTs ranges from 10.6% to 43% in the literature [1, 2, 6–8, 11, 16, 18, 19, 21, 23]. In our study, we did not identify any association between the mutation status of the GIST and occurrence of additional malignancy. This finding is in accordance with the literature, as no clear association for the molecular status of

Table 1 Case characteristics

		GIST only $N = 118$	GIST with associated NPL $N = 70$	*P* Value
Mean age [years] (range)	GIST diagnosis	62 (62–89)	69 (36–94)	*0.003*
	Secondary malignancy	–	66 (25–94)	
	First malignancy	–	65 (25–94)	
Gender f/m		1: 1.2	1: 1	
Location of GIST [*N*] (%)	Stomach	61 (51.7)	50 (71.4)	
	Small intestine	42 (35.6)	8 (11.4)	
	Colon and rectum	9 (7.6)	5 (7.1)	
	Other	6 (5.1)	7 (10.0)	*0.003*
GIST morphology [*N*] (%)	Spindle-shaped	99 (83.9)	55 (78.6)	
	Epithelioid	6 (5.1)	6 (8.6)	
	Mixed	5 (4.2)	5 (7.1)	
	N/A	8 (6.8)	4 (5.7)	0.623
T-stage of GIST [*N*] (%)	T1	17 (14.4)	20 (28.6)	
	T2	43 (37.3)	25 (35.7)	
	T3	20 (24.6)	12 (17.1)	
	T4	10 (8.5)	4 (5.7)	
	Tx	18 (15.3)	9 (12.9)	0.322
Risk stratification[a] [*N*] (%)	None	19 (16.1)	16 (22.9)	
	Very low	21 (17.8)	15 (21.4)	
	Low	28 (23.7)	9 (12.9)	
	Intermediate	18 (15.3)	9 (12.9)	
	High	25 (21.2)	6 (8.6)	
	Not evaluable	7 ((5.9)	13 (18.6)	*0.010*
Mitotic count [x/HPF] (mean) (range)		6 (0–100)	6 (0–64)	
	≤ 5/HPF [N]	83 (74)[c]	52 (81)[d]	
	> 5/HPF [N]	29 (26)[c]	12 (19)[d]	0.302

The collectives of GIST without and GIST with MaGs cases showed significant differences concerning mean age, the rate of occurrence in the small intestine, and risk classifications

Clinicopathological characteristics

[a] Miettinen

[b] Most common sites

[c] Information available in only 112 cases

[d] Information available in only 64 cases

KIT and PDGFRA has been found [8, 19]. We found significant differences concerning mean age, the rate of occurrence in the small intestine, and risk classifications ($P = 0.010$). In general, the GIST with MaGs showed lower aggressive features compared to GIST only cases. Therefore, it seems very likely that these findings represent not a causal relation. Patients with less aggressive GISTs just might have a higher chance to develop a further neoplasm.

The results of different studies including our results are summarized in Table 4. The molecular characteristics and their distributions of the GISTs are quite similar to what Corless et al. [4] reported for GISTs in general (Fig. 2a). The rate of *KIT* exon 11 mutations in the studies addressing MaGs might be a little lower and that of PDGFRA mutations somewhat higher compared to unstratified GISTs. However, this is speculative and would need confirmation in much larger studies or meta-analyses. Nevertheless, even if such a slide difference could be proven being significant, it is very unlikely that this could explain the higher rate of additional neoplasms in patients with GIST. This phenomenon, however, could be shown to be true by Murphy et al. who calculated a standardized prevalence ratio (SPR) of 7.51 of bladder carcinoma in cases of diagnosed GISTs. Other cancers with an SPR > 5 are esophageal adenocarcinoma and sarcomas (12.0 and 5.24). The highest standardized incidence ratios (SIRs) were found in ovarian cancers (8.72), small bowel adenocarcinomas (5.89), other female GU tumors (6.0), and papillary thyroid cancers (5.16). The SPR and SIR of all sites were 1.44 and 1.66, respectively [16].

Table 2 Distribution of entities and sites of MaGs and the mutations of the corresponding GISTs

Organ system and location of associated neoplasia					Histogenesis	Time sequence		Molecular aberration of the associated GIST						
						Time pre GIST [months] median (range)	Time second. GIST [months] median (range)	wt	KIT exon 9	KIT exon 11	KIT exon 13	PDGFRA exon 12	PDGFRA exon 18	n.a.
Skin/anoderm	*5*	*(7.1%)*				*278 (278)*	*28 (1–29)*	*1*		*3*			*1*	
Squamous cancer			1	(1.4%)	Epithelial					1				
Basal cell carcinoma			2	(2.9%)	Epithelial			1		1				
Melanoma			2	(2.9%)	Neurodermal					1			1	
Lung	*2*	*(2.9%)*				*n.a.*	*19 (5–33)*			*2*				
NSCLC			2	(2.9%)	Epithelial					2				
Gastrointestinal tract	*24*	*(34.3%)*				*3 (1–392)*	*66 (66–68)*	*1*	*2*	*12*		*1*	*2*	*6*
Esophagus			2	(2.9%)	Epithelial			1					1	
Stomach			7	(10.0%)	Epithelial				2	3				2
			1	(1.4%)	Neuroendocrine					1				
Colon			11	(15.7%)	epithelial					6		1		4
Rectum			1	(1.4%)	epithelial					1				
Appendix verm.			1	(1.4%)	Neuroendocrine					1				
Pancreas			1	(1.4%)	epithelial								1	
Breast/female tract	*14*	*(20.0%)*				*90 (8–434)*	*11 (7–35)*	*1*	*1*	*11*				*1*
Breast cancer			5	(7.1%)	Epithelial					5				
Endometrial cancer			4	(5.7%)	Epithelial			1	1	2				
ovarian cancer			2	(2.9%)	Epithelial					1				1
Squamous cancer (cervical, vulvar)			3	(4.3%)	Epithelial					3				
Urogenital tract	*17*	*(24.3%)*				*44 (2–116)*	*28 (1–71)*	*3*		*7*		*1*	*3*	*3*
Urothelial			2	(2.9%)	Epithelial					1				1
Kidney			8	(11.4%)	Epithelial					5			1	2
Prostate			6	(8.6%)	Epithelial			3				1	2	0
Seminoma			1	(1.4%)	Germ cell					1				
Blood/lymphatic system	*5*	*(7.1%)*				*55 (50–60)*	*16 (4–71)*			*1*	*1*		*1*	*2*
AML			1	(1.4%)	Myeloid					1				
CLL			1	(1.4%)	Lymphoid									1
Follicular Lymphoma			1	(1.4%)	Lymphoid						1			
Plasmocytoma			2	(2.9%)	Lymphoid								1	1
Others	*3*	*(4.3%)*				*2 (2)*	*73 (70–76)*	*1*		*1*				*1*
Pheochromocytoma			1	(1.4%)	Endocrine					1				

Table 2 (continued)

Organ system and location of associated neoplasia			Histogenesis	Time sequence		Molecular aberration of the associated GIST						
				Time pre GIST [months] median (range)	Time second. GIST [months] median (range)	wt	KIT exon 9	KIT exon 11	KIT exon 13	PDGFRA exon 12	PDGFRA exon 18	n.a.
Thymus carcinoma	1	(1.4%)	Epithelial			1						
CNS hemangiopericytoma /SFT (WHO III)	1	(1.4%)	Mesenchymal									1
	70					*7 (12.3%)*	*3 (5.3%)*	*37 (64.9%)*	*1 (1.8%)*	*2 (3.5%)*	*7 (12.3%)*	*13*

NSCLC non-small cell carcinoma, *AML* acute myeloid leukemia, *CLL* chronic lymphatic leukemia, *CNS* central nervous system, *SFT* solitary fibrous tumor

Concerning the site of secondary malignancies (Table 4), there is some variance in the reported distributions. The most striking is the rate of MaGs from the gastrointestinal tract with rates between 3% and 58%. In this context, the data of Murphy et al. are probably the most reliable ones because of their huge case number of more than 6000 cases [16]. In accordance with our data and that from several others, they report a high frequency of neoplasms from the urogenital tract [2, 6, 8]. This seems remarkable because in our series, all tumors except one from that site preceded the GISTs (Fig. 2c). Moreover, together with tumors from the breast and female genital tract, these tumors showed a higher frequency of third and fourth malignancies ($P = 0.046$) (Fig. 2b). The occurrence of both renal cancer and GIST has been addressed by Mendonca et al. who also reported a high rate of further malignancies in 55% of the cases [12].

An issue that has not been investigated well in the past is the potential role of time intervals between GISTs and secondary malignancies. Earlier studies investigated the time point of GIST diagnosis (before/after/simultaneously) to secondary malignancies [8, 11, 18, 19], but only one study further analyzed the exact time intervals [16]. The analysis of our data shows time intervals of about 4 years (median 50 months) between the occurrence of secondary malignancies and GIST if secondary malignancy preceded. If GIST is diagnosed first, secondary malignancies were frequently found within the first 3 years after GIST (median: 28.5 months) (Fig. 2). Murphy et al. demonstrated an increased rate of secondary malignancies within 5 years before/after GIST, as measured by standard prevalence/incidence ratio interpretations, while those rates were especially elevated within 1 year before/after GIST diagnosis itself. These authors observed a median time interval of 3.6 years for all patients. This aspect may be of clinical relevance, as it demonstrates the need for intensified tumor screening after GIST diagnosis [8, 19]. Taking into consideration that survival of patients is not affected by GIST, but significantly by the existence of secondary malignancy, the term "sentinel tumor," as suggested by Rodriguez et al., may act as good descriptor [11, 18–20]. These findings are supported by our results, which indicate that survival is not influenced by the GIST but by the secondary malignancy.

Although our study is still limited by a relatively small number of cases, it confirms the recently reported findings of an association of GIST with other neoplasms and the normal distribution of molecular aberrations known from GIST in general. Because we and others identified no molecular subtypes of GIST that are prone to be associated with additional cancers, the factors responsible for this association remain unclear. It can be hypothesized that a generally increased susceptibility for neoplasms exists in those patients. Further investigations, which should include whole-exome analyses and epigenetic investigations, are needed to elucidate the mechanisms leading to increased cancer susceptibility in GIST patients. Moreover,

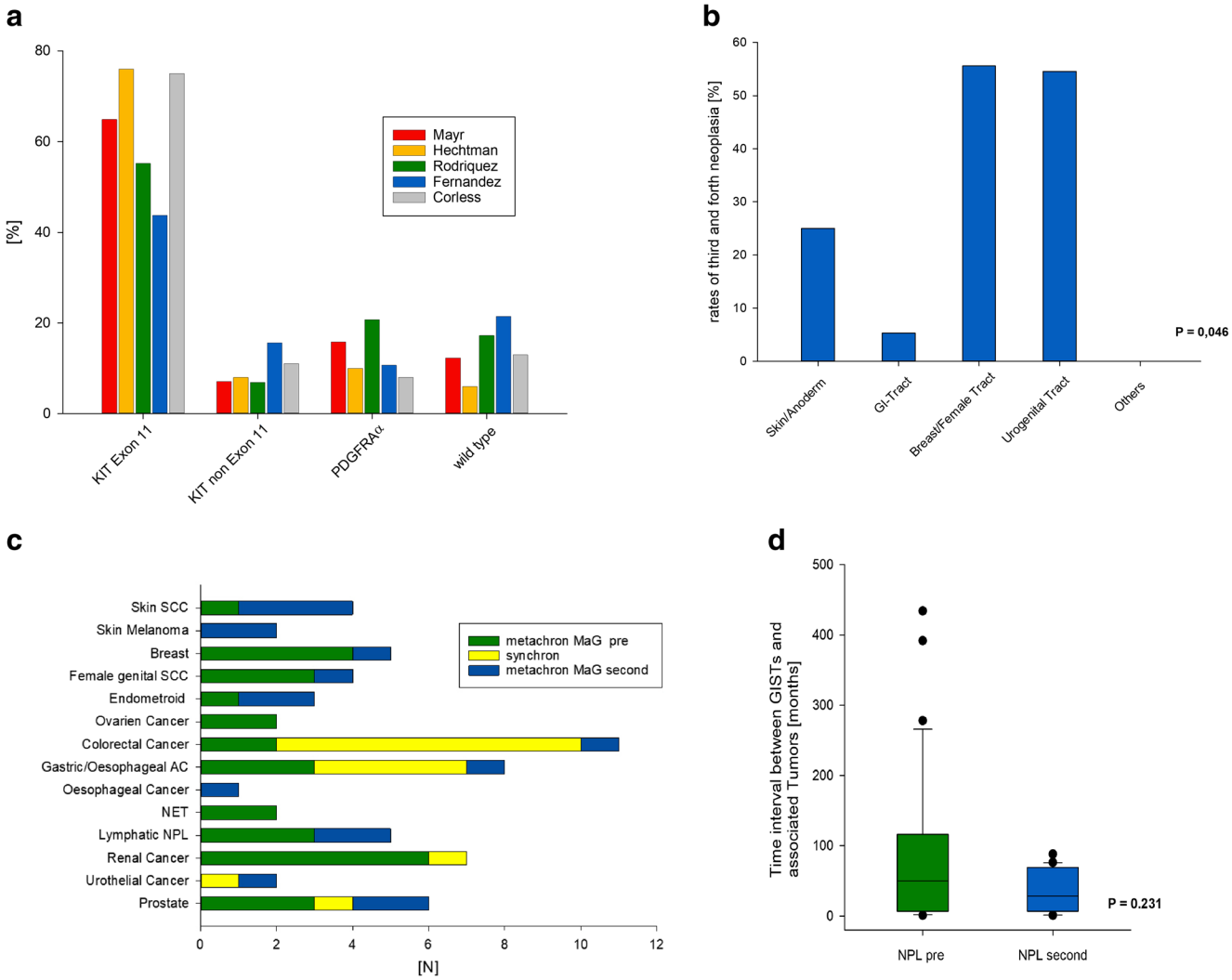

Fig. 2 **a** Distribution of mutations of our study and the results of the literature in comparison to the distribution in unselected GISTs (Corless et al.). **b** Rates of third and fourth malignancies dependent on the site of the first non-GIST. **c** Time sequence of the neoplasms. **d** Time interval between GIST and associated malignancies. *NPL pre = associated neoplasm previous to GIST*, *NPL second = associated neoplasm after GIST*, *SCC = squamous cell carcinoma*, *AC = adenocarcinoma*, *NET = neuroendocrine tumor*, *NPL = neoplasm*

Table 3 Distribution of entities and sites of third and fourth MaGs and the mutations of the corresponding GISTs

Organ system and location of second neoplasia	Mol. aberration of associated GIST	Organ system and location of third neoplasia	Organ system and location of fourth neoplasia
Skin/anoderm			
Basal cell carcinoma	wt	Ovarian carcinoma	
Gastrointestinal tract			
Colon cancer	KIT ex 11	Gastric cancer	
Breast/female tract			
Breast cancer	KIT ex 11	B-NHL	Breast cancer
	KIT ex 11	Lymphoplasmocytic NHL	MPN
Endometrial cancer	wt	NSCLC	
Ovarian cancer	na	Ovarian borderline tumor	Breast cancer
Squamous cancer (cervical, vulvar)	KIT ex 11	Gastric cancer	
Urogenital tract			
Renal cancer	KIT ex 11	Urothelial cancer	
Renal cancer	KIT ex 11	Prostate cancer	
Renal cancer	KIT ex 11	NSCLC	
Renal cancer	na	Gastroesophageal junction cancer	
Renal cancer	na	NSCLC	NET
Prostate cancer	PDFRA ex 18	Gastroesophageal junction cancer	unclear
Prostate cancer	na	Appendical goblet carcinoid	

B_NHL B-cell non-Hodgkins lymphoma, *NSCLC* non-small cell carcinoma, *MPN* myeloproliferative neoplasia, *NET* neuroendocrine tumor.

Table 4 Own results and data from the literature concerning rates, affected organ systems, and mutations of the corresponding GISTs

Author	Year	*N*	Rates of associated NPL			Organ systems affected by associated NPL											Molecular data			
			Rate of ass. NPL	Rate of tertiary NPL#	Rate of GISTs before other NPL	GI tract	Liver/ pancreas	Urogenital tract	Female genital tract	Breast	Blood/ lymphatic	Head and neck	Lung	Skin/ melanoma	Soft	Other	KIT 11	KIT non11	PDGFRA	WT
Hechtman et al. [8]	2015	260	19.2	14	24	3.3		36.7		13.3	13.3	11.7	1.7	5	5	10.1	76	8	10	6
Rodriquez et al. [19]	2016	128	35.9	8.7	17	37.8[a]	13,5[a]	8,1[a]	2,7[a]	5.4[a]	5.4[a]	0‡	8.1[a]	0[a]	5.4‡	10.8[a]	55.2	6.9	20.7	17.2
Fernández et al. [6]	2018	104	30.7			26	11.7	20.5		8.8	8.8	5.8	5.8	2.9	2.9	2.9	43.8	15.6	10.7	21.4
Mayr et al.		188	37.2	20	36.4	32.9	1.4	24.3	12.9	7.1	7.1	0	2.9	7.1	1.4	2.9	64.9	7.1	15.8	12.3
Agaimy et al. [1]	2006	4813	10.1	6		42.8	4.1	7.6	14.4	7.0	7.6		5.4	2.7		10.1				
Pandurengan et al. [18]	2010	783	20.3	12.6	34	21.5	4.3	9.7	23.2	8.1	6.5		5.4	5.4		16.6				
Goncalves et al. [7]	2010	101	13.8			57		14	14	7						7				
Vassos et al. [23]	2014	86	43			69		12			9.5			7		2.5				
Murphy et al. [16]	2015	6112	17.1		41.8	17.2		35.8		11.9	6.6		8.2							
Kramer et al. [11]	2015	979	33.4	16.9[b]	66	37.2	6.3	6.6	19.2	8.2	7.3		2.5	7.3		5.4				
Smith et al. [21]	2016	1705	10.6[c]	36.4[d]		58[e]	[e]	7[e]	7[e]	6[e]			11[e]							
Aghdassi et al. [2]	2018	104	31			42.1	10.5	21.1		18.4	5.3			2.6						

NPL neoplasm, *GI* gastrointestinal tract, # no. of the cases with secondary npl is the basis

[a] Malignant cases only

[b] Based on a subset of 836 patients

[c] Only synchronous and npls after GIST included

[d] Calculated based on the publication b.t.o.k.

[e] npls within 6 months after GIST diagnosis, colorectal, and other GI locations are grouped together

as long as these mechanisms are undetected, surveillance of even low-risk GIST patients may be justified.

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Authors' contributions Patrick Mayr: study design, data acquisition and interpretation, manuscript drafting. Bruno Märkl: manuscript drafting and study design.Abbas Agaimy: manuscript drafting and data interpretation. Bernadette Kriening: data acquisition. Sebastian Dintner: data analysis and data acquisition. Gerhard Schenkirsch: data acquisition. Regine Schneider-Stock: study design, data acquisition and interpretation, and manuscript drafting.

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Compliance with ethical standards

This study was approved by the ethical board of Klinikum Augsburg.

Conflict of interest The authors declare that they have no conflict of interest.

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